

## General

### Guideline Title

KDIGO clinical practice guideline for anemia in chronic kidney disease.

### Bibliographic Source(s)

Kidney Disease: Improving Global Outcomes (KDIGO) Anemia Work Group. KDIGO clinical practice guideline for anemia in chronic kidney disease. *Kidney Int Suppl.* 2012 Aug;2(4):279-335. [247 references]

### Guideline Status

This is the current release of the guideline.

## Recommendations

### Major Recommendations

Definitions of the strength of recommendation (Level 1, Level 2, or Not Graded), and the quality of the supporting evidence (A-D) are provided at the end of the 'Major Recommendations' field.

#### Diagnosis and Evaluation of Anemia in Chronic Kidney Disease (CKD)

##### Testing for Anemia

##### *Frequency of Testing for Anemia*

- For CKD patients without anemia (as defined in the recommendations below for adults and children), measure hemoglobin (Hb) concentration when clinically indicated and (*Not Graded*):
  - At least annually in patients with CKD 3
  - At least twice per year in patients with CKD 4–5 non-dialysis-dependent (ND)
  - At least every 3 months in patients with CKD 5 hemodialysis-dependent (HD) and CKD 5 peritoneal dialysis-dependent (PD)
- For CKD patients with anemia not being treated with an erythropoiesis-stimulating agent (ESA), measure Hb concentration when clinically indicated and (*Not Graded*):
  - At least every 3 months in patients with CKD 3–5ND and CKD 5PD
  - At least monthly in patients with CKD 5HD

See recommendations below for measurement of Hb concentration in patients being treated with ESA.

##### *Diagnosis of Anemia*

- Diagnose anemia in adults and children >15 years with CKD when the Hb concentration is <13.0 g/dl (<130 g/l) in males and <12.0 g/dl

(<120 g/l) in females. (*Not Graded*)

- Diagnose anemia in children with CKD if Hb concentration is <11.0 g/dl (<110 g/l) in children 0.5–5 years, <11.5 g/dl (115 g/l) in children 5–12 years, and <12.0 g/dl (120 g/l) in children 12–15 years. (*Not Graded*)

### *Investigation of Anemia*

- In patients with CKD and anemia (regardless of age and CKD stage), include the following tests in initial evaluation of the anemia (*Not Graded*):
  - Complete blood count (CBC), which should include Hb concentration, red cell indices, white blood cell count and differential, and platelet count
  - Absolute reticulocyte count
  - Serum ferritin level
  - Serum transferrin saturation (TSAT)
  - Serum vitamin B<sub>12</sub> and folate levels

### Use of Iron to Treat Anemia in CKD

#### Treatment with Iron Agents

- When prescribing iron therapy, balance the potential benefits of avoiding or minimizing blood transfusions, ESA therapy, and anemia-related symptoms against the risks of harm in individual patients (e.g., anaphylactoid and other acute reactions, unknown long-term risks). (*Not Graded*)
- For adult CKD patients with anemia not on iron or ESA therapy, the Work Group suggests a trial of intravenous (IV) iron (or in CKD ND patients alternatively a 1–3 month trial of oral iron therapy) if (2C):
  - An increase in Hb concentration without starting ESA treatment is desired\* and
  - TSAT is ≤30% and ferritin is ≤500 ng/ml (≤500 µg/l)
- For adult CKD patients on ESA therapy who are not receiving iron supplementation, the Work Group suggests a trial of IV iron (or in CKD ND patients alternatively a 1–3 month trial of oral iron therapy) if (2C):
  - An increase in Hb concentration\*\* or a decrease in ESA dose is desired\*\*\* and
  - TSAT is ≤30% and ferritin is ≤500 ng/ml (≤500 µg/l)
- For CKD ND patients who require iron supplementation, select the route of iron administration based on the severity of iron deficiency, availability of venous access, response to prior oral iron therapy, side effects with prior oral or IV iron therapy, patient compliance, and cost. (*Not Graded*)
- Guide subsequent iron administration in CKD patients based on Hb responses to recent iron therapy, as well as ongoing blood losses, iron status tests (TSAT and ferritin), Hb concentration, ESA responsiveness and ESA dose in ESA treated patients, trends in each parameter, and the patient's clinical status. (*Not Graded*)
- For all pediatric CKD patients with anemia not on iron or ESA therapy, the Work Group recommends oral iron (or IV iron in CKD HD patients) administration when TSAT is ≤20% and ferritin is ≤100 ng/ml (≤100 µg/l). (*ID*)
- For all pediatric CKD patients on ESA therapy who are not receiving iron supplementation, the Work Group recommends oral iron (or IV iron in CKD HD patients) administration to maintain TSAT >20% and ferritin >100 ng/ml (>100 µg/l). (*ID*)

\*Based on patient symptoms and overall clinical goals, including avoidance of transfusion, improvement in anemia-related symptoms, and after exclusion of active infection.

\*\*Consistent with recommendations below under 'ESA Initiation.'

\*\*\*Based on patient symptoms and overall clinical goals including avoidance of transfusion and improvement in anemia-related symptoms, and after exclusion of active infection and other causes of ESA hyporesponsiveness.

#### Iron Status Evaluation

- Evaluate iron status (TSAT and ferritin) at least every 3 months during ESA therapy, including the decision to start or continue iron therapy. (*Not Graded*)
- Test iron status (TSAT and ferritin) more frequently when initiating or increasing ESA dose, when there is blood loss, when monitoring response after a course of IV iron, and in other circumstances where iron stores may become depleted. (*Not Graded*)

#### Cautions Regarding Iron Therapy

- When the initial dose of IV iron dextran is administered, the Work Group recommends (*IB*) and when the initial dose of IV nondextran iron is administered, the Work Group suggests (2C) that patients be monitored for 60 minutes after the infusion, and that resuscitative facilities (including medications) and personnel trained to evaluate and treat serious adverse reactions be available.

## Iron During Infection

- Avoid administering IV iron to patients with active systemic infections. (*Not Graded*)

## Use of ESAs and Other Agents to Treat Anemia in CKD

### ESA Initiation

- Address all correctable causes of anemia (including iron deficiency and inflammatory states) prior to initiation of ESA therapy. (*Not Graded*)
- In initiating and maintaining ESA therapy, the Work Group recommends balancing the potential benefits of reducing blood transfusions and anemia-related symptoms against the risks of harm in individual patients (e.g., stroke, vascular access loss, hypertension). (*1B*)
- The Work Group recommends using ESA therapy with great caution, if at all, in CKD patients with active malignancy—in particular when cure is the anticipated outcome—(*1B*), a history of stroke (*1B*), or a history of malignancy. (*2C*)
- For adult CKD ND patients with Hb concentration  $\geq 10.0$  g/dl ( $\geq 100$  g/l), the Work Group suggests that ESA therapy not be initiated. (*2D*)
- For adult CKD ND patients with Hb concentration  $< 10.0$  g/dl ( $< 100$  g/l), the Work Group suggests that the decision whether to initiate ESA therapy be individualized based on the rate of fall of Hb concentration, prior response to iron therapy, the risk of needing a transfusion, the risks related to ESA therapy and the presence of symptoms attributable to anemia. (*2C*)
- For adult CKD 5D patients, the Work Group suggests that ESA therapy be used to avoid having the Hb concentration fall below 9.0 g/dl (90 g/l) by starting ESA therapy when the hemoglobin is between 9.0–10.0 g/dl (90–100 g/l). (*2B*)
- Individualization of therapy is reasonable as some patients may have improvements in quality of life at higher Hb concentration and ESA therapy may be started above 10.0 g/dl (100 g/l). (*Not Graded*)
- For all pediatric CKD patients, the Work Group suggests that the selection of Hb concentration at which ESA therapy is initiated in the individual patient includes consideration of potential benefits (e.g., improvement in quality of life, school attendance/performance, and avoidance of transfusion) and potential harms. (*2D*)

### ESA Maintenance Therapy

- In general, the Work Group suggests that ESAs not be used to maintain Hb concentration above 11.5 g/dl (115 g/l) in adult patients with CKD. (*2C*)
- Individualization of therapy will be necessary as some patients may have improvements in quality of life at Hb concentration above 11.5 g/dl (115 g/l) and will be prepared to accept the risks. (*Not Graded*)
- In all adult patients, the Work Group recommends that ESAs not be used to intentionally increase the Hb concentration above 13 g/dl (130 g/l). (*1A*)
- In all pediatric CKD patients receiving ESA therapy, the Work Group suggests that the selected Hb concentration be in the range of 11.0 to 12.0 g/dl (110 to 120 g/l). (*2D*)

### ESA Dosing

- The Work Group recommends determining the initial ESA dose using the patient's Hb concentration, body weight, and clinical circumstances. (*1D*)
- The Work Group recommends that ESA dose adjustments be made based on the patient's Hb concentration, rate of change in Hb concentration, current ESA dose and clinical circumstances. (*1B*)
- The Work Group suggests decreasing ESA dose in preference to withholding ESA when a downward adjustment of Hb concentration is needed. (*2C*)
- Re-evaluate ESA dose if (*Not Graded*):
  - The patient suffers an ESA-related adverse event
  - The patient has an acute or progressive illness that may cause ESA hyporesponsiveness (see 'Initial ESA Hyporesponsiveness,' below)

### ESA Administration

- For CKD 5HD patients and those on hemofiltration or hemodiafiltration therapy, the Work Group suggests either intravenous or subcutaneous administration of ESA. (*2C*)
- For CKD ND and CKD 5PD patients, the Work Group suggests subcutaneous administration of ESA. (*2C*)

## Frequency of Administration

- The Work Group suggests determining the frequency of ESA administration based on CKD stage, treatment setting, efficacy considerations, patient tolerance and preference, and type of ESA. (2C)

### Type of ESA

- The Work Group recommends choosing an ESA based on the balance of pharmacodynamics, safety information, clinical outcome data, costs, and availability. (1D)
- The Work Group suggests using only ESAs that have been approved by an independent regulatory agency. Specifically for 'copy' versions of ESAs, true biosimilar products should be used. (2D)

### Evaluating and Correcting Persistent Failure to Reach or Maintain Intended Hemoglobin Concentration

#### *Frequency of Monitoring*

- During the initiation phase of ESA therapy, measure Hb concentration at least monthly. (Not Graded)
- For CKD ND patients, during the maintenance phase of ESA therapy measure Hb concentration at least every 3 months. (Not Graded)
- For CKD 5D patients, during the maintenance phase of ESA therapy measure Hb concentration at least monthly. (Not Graded)

#### *Initial ESA Hyporesponsiveness*

- Classify patients as having ESA hyporesponsiveness if they have no increase in Hb concentration from baseline after the first month of ESA treatment on appropriate weight-based dosing. (Not Graded)
- In patients with ESA hyporesponsiveness, the Work Group suggests avoiding repeated escalations in ESA dose beyond double the initial weight-based dose. (2D)

#### *Subsequent ESA Hyporesponsiveness*

- Classify patients as having acquired ESA hyporesponsiveness if after treatment with stable doses of ESA, they require 2 increases in ESA doses up to 50% beyond the dose at which they had been stable in an effort to maintain a stable Hb concentration. (Not Graded)
- In patients with acquired ESA hyporesponsiveness, the Work Group suggests avoiding repeated escalations in ESA dose beyond double the dose at which they had been stable. (2D)

#### *Management of Poor ESA Responsiveness*

- Evaluate patients with either initial or acquired ESA hyporesponsiveness and treat for specific causes of poor ESA response. (Not Graded)
- For patients who remain hyporesponsive despite correcting treatable causes, the Work Group suggests individualization of therapy, accounting for relative risks and benefits of (2D):
  - Decline in Hb concentration
  - Continuing ESA, if needed to maintain Hb concentration, with due consideration of the doses required
  - Blood transfusions

### Adjuvant Therapies

- The Work Group recommends not using androgens as an adjuvant to ESA treatment. (1B)
- The Work Group suggests not using adjuvants to ESA treatment including vitamin C, vitamin D, vitamin E, folic acid, L-carnitine, and pentoxifylline. (2D)

### Evaluation for Pure Red Cell Aplasia (PRCA)

- Investigate for possible antibody-mediated PRCA when a patient receiving ESA therapy for more than 8 weeks develops the following (Not Graded):
  - Sudden rapid decrease in Hb concentration at the rate of 0.5 to 1.0 g/dl (5 to 10 g/l) per week OR requirement of transfusions at the rate of approximately 1 to 2 per week, AND
  - Normal platelet and white cell counts, AND
  - Absolute reticulocyte count less than 10,000/ $\mu$ l
- The Work Group recommends that ESA therapy be stopped in patients who develop antibody-mediated PRCA. (1A)
- The Work Group recommends peginesatide be used to treat patients with antibody-mediated PRCA. (1B)

### Red Cell Transfusion to Treat Anemia in CKD

## Use of Red Cell Transfusion in Chronic Anemia

- When managing chronic anemia, the Work Group recommends avoiding, when possible, red cell transfusions to minimize the general risks related to their use. (1B)
- In patients eligible for organ transplantation, the Work Group specifically recommends avoiding, when possible, red cell transfusions to minimize the risk of allosensitization. (1C)
- When managing chronic anemia, the Work Group suggests that the benefits of red cell transfusions may outweigh the risks in patients in whom (2C):
  - ESA therapy is ineffective (e.g., hemoglobinopathies, bone marrow failure, ESA resistance)
  - The risks of ESA therapy may outweigh its benefits (e.g., previous or current malignancy, previous stroke)
- The Work Group suggests that the decision to transfuse a CKD patient with non-acute anemia should not be based on any arbitrary Hb threshold, but should be determined by the occurrence of symptoms caused by anemia. (2C)

## Urgent Treatment of Anemia

- In certain acute clinical situations, the Work Group suggests patients are transfused when the benefits of red cell transfusions outweigh the risks; these include (2C):
  - When rapid correction of anemia is required to stabilize the patient's condition (e.g., acute hemorrhage, unstable coronary artery disease)
  - When rapid pre-operative Hb correction is required

## Definitions:

## Nomenclature and Description for Grading Recommendations

Implications			
Grade*	Patients	Clinicians	Policy
Level 1 'The Work Group recommends'	Most people in your situation would want the recommended course of action and only a small proportion would not.	Most patients should receive the recommended course of action.	The recommendation can be evaluated as a candidate for developing a policy or a performance measure.
Level 2 'The Work Group suggests'	The majority of people in your situation would want the recommended course of action, but many would not.	Different choices will be appropriate for different patients. Each patient needs help to arrive at a management decision consistent with her or his values and preferences.	The recommendation is likely to require debate and involvement of stakeholders before policy can be determined.

\*The additional category 'Not Graded' was used, typically, to provide guidance based on common sense or where the topic does not allow adequate application of evidence. The most common examples include recommendations regarding monitoring intervals, counseling, and referral to other clinical specialists. The ungraded recommendations are generally written as simple declarative statements, but are not meant to be interpreted as being stronger recommendations than Level 1 or 2 recommendations.

## Final Grade for Overall Quality of Evidence

Grade	Quality of Evidence	Meaning
A	High	The Work Group is confident that the true effect lies close to that of the estimate of the effect.
B	Moderate	The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
C	Low	The true effect may be substantially different from the estimate of the effect.
D	Very Low	The estimate of effect is very uncertain, and often will be far from the truth.

## Clinical Algorithm(s)

An algorithm for red cell transfusion use in chronic kidney disease (CKD) patients is available in the original guideline document.

# Scope

## Disease/Condition(s)

Anemia in chronic kidney disease

## Guideline Category

Diagnosis

Evaluation

Management

Treatment

## Clinical Specialty

Cardiology

Endocrinology

Hematology

Internal Medicine

Nephrology

Oncology

Pathology

Pediatrics

## Intended Users

Advanced Practice Nurses

Health Care Providers

Nurses

Pharmacists

Physician Assistants

Physicians

## Guideline Objective(s)

- To provide guidance on diagnosis, evaluation, management and treatment for all chronic kidney disease (CKD) patients (non-dialysis, dialysis, kidney transplant recipients and children) at risk of or with anemia
- To improve patient care by helping clinicians know and better understand the evidence (or lack of evidence) that determines current practice
- To assist the practitioner caring for patients with CKD and anemia and to prevent deaths, cardiovascular disease events and progression to kidney failure while optimizing patients' quality of life

## Target Population

Patients (adult and children) with chronic kidney disease at risk for or with anemia

## Interventions and Practices Considered

### Diagnosis/Evaluation

1. Frequency of testing for anemia in chronic kidney disease (CKD) patients
2. Diagnosis of anemia based on hemoglobin (Hb) concentration
3. Other investigations
  - Complete blood count (CBC), including Hb concentration, red cell indices, white blood cell count and differential, and platelet count
  - Absolute reticulocyte count
  - Serum ferritin level
  - Serum transferrin saturation (TSAT)
  - Serum vitamin B<sub>12</sub> and folate levels

### Treatment/Management

1. Iron supplementation (oral or intravenous)
2. Iron status evaluation (TSAT and ferritin)
3. Monitoring for adverse effects
4. Use of erythropoiesis-stimulating agents (ESA) (initiation and maintenance dosing, type of ESA, and frequency of administration)
5. Evaluating and correcting persistent failure to reach or maintain intended hemoglobin concentration
6. Adjuvant therapies, such as androgens, vitamin C, vitamin D, vitamin E, folic acid, L-carnitine, and pentoxifylline (not recommended)
7. Evaluation for pure red cell aplasia (PRCA)
8. Stopping ESA in PRCA
9. Peginesatide to treat patients with antibody-mediated PRCA
10. Use of red cell transfusion
11. Urgent treatment of anemia

## Major Outcomes Considered

- All-cause mortality
- Cardiovascular events
- End-stage renal disease (ESRD)
- Quality of life
- Progression of kidney disease
- Transfusion requirements
- Major symptoms
- Adverse events

## Methodology

### Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Searches of Electronic Databases

### Description of Methods Used to Collect/Select the Evidence

## Literature Searches and Article Selection

The Work Group sought to build on the evidence base and topics addressed in the previous Kidney Disease Outcomes Quality Initiative (KDOQI) clinical practice guidelines and clinical practice recommendations for anemia in chronic kidney disease in 2006 as well as the KDOQI clinical practice guidelines and clinical practice recommendations for anemia in chronic kidney disease 2007 update of hemoglobin target. Modules were created for randomized controlled trials (RCTs), kidney disease, anemia, and erythropoietin, transfusion, iron deficiency, and adjuvant search terms. The search terms were then limited to years 2006–2010 for studies related to anemia interventions. For transfusion the literature search was conducted from 1989–2010. A separate search was run for observational studies on iron overload and hemoglobin status as predictors for clinical outcomes (see Appendix 1 in the supplemental appendices; see the 'Availability of Companion Documents' field).

The searches were run in MEDLINE, Cochrane Central Register of Controlled Clinical Trials and Cochrane Database of Systematic Reviews. The initial search for RCTs was conducted in April 2010 and subsequently updated in October of 2010. The search for observational studies was later conducted in September 2010. The search yield was also supplemented by articles provided by Work Group members through March 2012. MEDLINE search results were screened by members of the ERT for relevance using pre-defined eligibility criteria.

The total yield from the search was 4,334 abstracts for RCTs and 3,717 abstracts for observational studies. Fifty-six abstracts and 53 full texts from RCTs were accepted and 97 abstracts and 21 full texts from observational studies were accepted. Journal articles reporting original data, meta-analyses or systematic reviews were selected for evidence review. Editorials, letters, abstracts, unpublished reports and articles published in non-peer reviewed journals were not included. The Work Group also decided to exclude publications from journal supplements because of potential differences in the process of how they get solicited, selected, reviewed and edited compared to peer-reviewed publications.

### Limitations of Approach

While the literature searches were intended to be comprehensive, they were not exhaustive. MEDLINE was the only database searched. Hand searches of journals were not performed, and review articles and textbook chapters were not systematically searched. However, important studies known to domain experts that were missed by the electronic literature searches were added to retrieved articles and reviewed by the Work Group.

## Number of Source Documents

The overall search yield along with the number of abstracts identified and articles reviewed is presented in Table 10 in the original guideline document. Fifty-six abstracts and 53 full texts from randomized controlled trials (RCTs) were accepted and 97 abstracts and 21 full texts from observational studies were accepted.

## Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

### Rating Scheme for the Strength of the Evidence

Grading of Recommendations Assessment, Development and Evaluation (GRADE) System for Grading Quality of Evidence for an Outcome

Step 1: Starting Grade for Quality of Evidence Based on Study Design	
Randomized trials	High
Observational study	Low
Any other evidence	Very low
Step 2: Reduce Grade	
Study quality	-1 level if serious limitations -2 levels if very serious limitations
Consistency	-1 level if important inconsistency
Directness	-1 level if some uncertainty -2 levels if major uncertainty

Other	-1 level if sparse or imprecise data -1 level if high probability of reporting bias
<b>Step 3: Raise Grade</b>	
Strength of association	+1 level if strong, <sup>a</sup> no plausible confounders +2 levels if very strong, <sup>b</sup> no major threats to validity
Other	+1 level if evidence of a dose–response gradient +1 level if all residual plausible confounders would have reduced the observed effect
<b>Final Grade for Quality of Evidence and Definition</b>	
High	Further research is unlikely to change confidence in the estimate of the effect
Moderate	Further research is likely to have an important impact on confidence in the estimate of effect, and may change the estimate
Low	Further research is very likely to have an important impact on confidence in the estimate, and may change the estimate
Very low	Any estimate of effect is very uncertain

<sup>a</sup>Strong evidence of association is defined as 'significant relative risk (RR) of >2 (<0.5)' based on consistent evidence from two or more observational studies, with no plausible confounders.

<sup>b</sup>Very strong evidence of association is defined as 'significant RR of >5 (<0.2)' based on direct evidence with no major threats to validity.

<sup>c</sup>Sparse if there is only one study or if total N <100. Imprecise if there is a low event rate (0 or 1 event) in either arm or confidence interval spanning a range <0.5 to >2.0.

Modified with permission from Uhlig et al. Grading evidence and recommendations for clinical practice guidelines in nephrology. A position statement from Kidney Disease: Improving Global Outcomes (KDIGO). Kidney Int 2006; 70: 2058–2065; and Atkins et al. Grading quality of evidence and strength of recommendations. BMJ 2004; 328: 1490.

#### Final Grade for Overall Quality of Evidence

Grade	Quality of Evidence	Meaning
A	High	The Work Group is confident that the true effect lies close to that of the estimate of the effect.
B	Moderate	The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
C	Low	The true effect may be substantially different from the estimate of the effect.
D	Very Low	The estimate of effect is very uncertain, and often will be far from the truth.

## Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

## Description of the Methods Used to Analyze the Evidence

### Data Extraction

Fifty-three full text articles from randomized controlled trials (RCTs) were extracted by the Evidence Review Team (ERT). The ERT, in consultation with the Work Group, designed forms to capture data on design, methodology, sample characteristics, interventions, comparators, outcomes, results and limitations of individual studies. Methodology and outcomes were also systematically graded (see the section on grading below) and recorded during the data extraction process.

### Summary Tables

Summary tables were developed for each comparison of interest. Studies included in the evidence base for the Kidney Disease Outcomes Quality Initiative (KDOQI) clinical practice guidelines on Anemia in Chronic Kidney Disease (CKD) and update of hemoglobin target were also incorporated if they fulfilled the inclusion criteria for the current guideline.

Summary tables contain outcomes of interest, relevant population characteristics, description of intervention and comparator, results, and quality

grading for each outcome. Categorical and continuous outcomes were summarized separately. Work Group members proofed all summary table data and quality assessments. Summary tables are available (see the 'Availability of Companion Documents' field).

## Evidence Profiles

Evidence profiles were constructed to assess and record quality grading and description of effect for each outcome across studies, and quality of overall evidence and description of net benefits or harms of intervention or comparator across all outcomes. These profiles aim to make the evidence synthesis process transparent. Decisions in the evidence profiles were based on data from the primary studies listed in corresponding summary tables, and on judgments of the ERT and the Work Group. When the body of evidence for a particular comparison of interest consisted of only one study, the summary table provided the final level of synthesis and evidence profile was not generated. Each evidence profile was initially constructed by the ERT and then reviewed, edited and approved by the Work Group.

## Rating the Quality of Evidence

A structured approach, based on Grading of Recommendations Assessment, Development and Evaluation (GRADE) and facilitated by the use of evidence profiles was used in order to grade the quality of the overall evidence. For each topic, the discussion on grading of the quality of the evidence was led by the ERT, and the discussion regarding the strength of the recommendations was led by the Work Group Chairs. The 'quality of a body of evidence' refers to the extent to which our confidence in an estimate of effect is sufficient to support a particular recommendation.

## Grading the Quality of Evidence for Each Outcome

Following GRADE, the quality of a body of evidence pertaining to a particular outcome of interest was initially categorized based on study design. For questions of interventions, the initial quality grade was 'High' when the body of evidence consisted of randomized controlled trials; 'Low', if it consisted of observational studies; or 'Very Low', if it consisted of studies of other study designs. For questions of interventions, the Work Group decided to use only randomized controlled trials. The grade for the quality of evidence for each intervention/outcome pair was then lowered if there were serious limitations to the methodological quality of the aggregate of studies, if there were important inconsistencies in the results across studies, if there was uncertainty about the directness of evidence including limited applicability of the findings to the population of interest, if the data were imprecise (a low event rate [0 or 1 event] in either arm or confidence interval spanning a range  $<0.5$  to  $>2.0$ ) or sparse (only 1 study or total  $N < 100$ ), or if there was thought to be a high likelihood of bias. The final grade for the quality of the evidence for an intervention/outcome pair could be one of the following four grades: 'High', 'Moderate', 'Low' or 'Very Low' (see the 'Rating Scheme for the Strength of the Evidence' field).

## Grading the Overall Quality of Evidence

The quality of the overall body of evidence was then determined based on the quality grades for all outcomes of interest, taking into account explicit judgments about the relative importance of each outcome. The resulting four final categories for the quality of overall evidence were: 'A', 'B', 'C' or 'D' (see the 'Rating Scheme for the Strength of the Evidence' field).

See the original guideline document for discussion of grading of quality of evidence for individual studies and assessment of net health benefit across all important clinical outcomes.

# Methods Used to Formulate the Recommendations

## Expert Consensus

# Description of Methods Used to Formulate the Recommendations

## Overview Process

The Work Group, Kidney Disease: Improving Global Outcomes (KDIGO) Co-Chairs, Evidence Review Team (ERT), and KDIGO support staff met for two 2-day meetings for training in the guideline development process, topic discussion, and consensus development.

## Commissioning of Work Group and Evidence Review Team

KDIGO Co-Chairs appointed the Work Group Co-chairs. Work Group Co-Chairs then assembled the Work Group consisting of domain experts, including individuals with expertise in internal medicine, adult and pediatric nephrology, cardiology, hematology, oncology, hypertension, pathology, pharmacology, epidemiology and endocrinology. Tufts Center for Kidney Disease Guideline Development and Implementation at Tufts Medical Center in Boston, Massachusetts, USA was contracted to conduct systematic evidence review and provide expertise in guideline

development methodology. The ERT consisted of physician-methodologists with expertise in nephrology, a project coordinator and manager, and a research assistant. The ERT instructed and advised Work Group members in all steps of literature review, critical literature appraisal, and guideline development. The Work Group and the ERT collaborated closely throughout the project.

### Defining Scope and Topics

Work Group Co-Chairs first defined the overall scope and goals of the guideline. Work Group Co-Chairs then drafted a preliminary list of topics and key clinical questions. In light of new evidence, it was decided that an update of the topics presented in the 2006 and 2007 Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines would be the best approach. The Work Group and ERT further developed and refined each topic, specified screening criteria, literature search strategies, and data extraction forms (see Table 8 in the original guideline document).

### Establishing the Process for Guideline Development

The ERT performed literature searches, organized abstract and article screening. The ERT also coordinated the methodological and analytic process of the report, defined and standardized the methodology of performing literature searches, data extraction, and summarizing the evidence. Throughout the project, the ERT offered suggestions for guideline development, led discussions on systematic review, literature searches, data extraction, assessment of quality and applicability of articles, evidence synthesis, grading of evidence and guideline recommendations, and consensus development. The Work Group took the primary role of writing the guidelines and rationale statements and retained final responsibility for the content of the guideline statements and the accompanying narrative.

The Work Group Co-Chairs prepared the first draft of the scope of work document as a series of topics to be considered by Work Group members. The scope of work document was based primarily on the existing KDOQI guidelines on anemia. At their first two-day meeting, Work Group members revised the initial working document to include all topics of interest to the Work Group. The inclusive, combined set of questions formed the basis for the deliberation and discussion that followed. The Work Group strove to ensure that all topics deemed clinically relevant and worthy of review were identified and addressed.

### Formulating Questions of Interest

Questions of interest were formulated according to the PICODD (Population, Intervention, Comparator, Outcome, study Design and Duration of follow up) criteria. Details of the PICODD criteria are presented in Table 8 in the original guideline document.

### Ranking of Outcomes

The Work Group ranked outcomes of interest based on their importance for informing clinical decision making (see Table 9 in the original guideline). Mortality, cardiovascular mortality, cardiovascular events and end-stage renal disease (ESRD) outcomes were graded as 'critical,' transfusion and quality of life (QoL) outcomes were graded as 'high,' and all other outcomes were graded as 'moderate.'

### Grading the Strength of the Recommendations

The strength of a recommendation is graded as Level 1 or Level 2. The 'Rating Scheme for the Strength of the Recommendations' field shows the Kidney Disease: Improving Global Outcomes (KDIGO) nomenclature for grading the strength of a recommendation and the implications of each level for patients, clinicians and policy makers. Recommendations can be for or against doing something. Table 16 in the original guideline document shows that the strength of a recommendation is determined not just by the quality of the evidence, but also by other, often complex judgments regarding the size of the net medical benefit, values and preferences, and costs. Formal decision analyses including cost analysis were not conducted.

### Ungraded Statements

This category was designed to allow the Work Group to issue general advice. Typically an ungraded statement meets the following criteria: it provides guidance based on common sense; it provides reminders of the obvious; it is not sufficiently specific to allow application of evidence to the issue and therefore it is not based on systematic evidence review. Common examples include recommendations about frequency of testing, referral to specialists, and routine medical care. The Work Group strove to minimize the use of ungraded recommendations.

This grading scheme with two levels for the strength of a recommendation together with four levels of grading the quality of the evidence, and the option of an ungraded statement for general guidance was adopted by the KDIGO Board in December 2008. The Work Group took the primary role of writing the recommendations and rationale statements and retained final responsibility for the content of the guideline statements and the accompanying narrative. The ERT reviewed draft recommendations and grades for consistency with the conclusions of the evidence review.

# Rating Scheme for the Strength of the Recommendations

## Nomenclature and Description for Grading Recommendations

Implications			
Grade*	Patients	Clinicians	Policy
Level 1 'The Work Group recommends'	Most people in your situation would want the recommended course of action and only a small proportion would not.	Most patients should receive the recommended course of action.	The recommendation can be evaluated as a candidate for developing a policy or a performance measure.
Level 2 'The Work Group suggests'	The majority of people in your situation would want the recommended course of action, but many would not.	Different choices will be appropriate for different patients. Each patient needs help to arrive at a management decision consistent with her or his values and preferences.	The recommendation is likely to require debate and involvement of stakeholders before policy can be determined.

\*The additional category 'Not Graded' was used, typically, to provide guidance based on common sense or where the topic does not allow adequate application of evidence. The most common examples include recommendations regarding monitoring intervals, counseling, and referral to other clinical specialists. The ungraded recommendations are generally written as simple declarative statements, but are not meant to be interpreted as being stronger recommendations than Level 1 or 2 recommendations.

## Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

## Method of Guideline Validation

External Peer Review

Internal Peer Review

## Description of Method of Guideline Validation

The guideline draft was sent for peer review to the Kidney Disease: Improving Global Outcomes (KDIGO) Board of Directors in June 2011, and for public review in September 2011.

### Summary of the Methodological Review Process

Several tools and checklists have been developed to assess the quality of the methodological process for systematic review and guideline development. These include the Appraisal of Guidelines for Research and Evaluation (AGREE) criteria, the Conference on Guideline Standardization (COGS) checklist, and the Institute of Medicine's recent *Standards for Systematic Reviews and Clinical Practice Guidelines We Can Trust*. Table 17 in the original guideline document and Appendix 2 online (see the 'Availability of Companion Documents' field) show, respectively, the COGS criteria which correspond to the AGREE checklist and the Institute of Medicine standards, and how each one of them is addressed in this guideline.

## Evidence Supporting the Recommendations

### Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see the 'Major Recommendations' field).

## Benefits/Harms of Implementing the Guideline Recommendations

## Potential Benefits

Safe and effective management of patients with anemia in chronic kidney disease

## Potential Harms

- Oral iron is inexpensive, readily available, and does not require intravenous (IV) access, a particular concern in chronic kidney disease (CKD) patients not on hemodialysis. It is also not associated with severe adverse effects but gastrointestinal side effects are common and may limit adherence. This, along with variable gastrointestinal tract absorption, limits the efficacy of oral iron. IV iron avoids concerns about medication adherence and efficacy in treating iron deficiency, but requires IV access and has been associated with infrequent but severe adverse reactions. Decisions about the preferred route of iron supplementation should take into consideration severity of anemia and iron deficiency, the response, tolerance and adherence to prior oral iron administration, costs, and ease of obtaining venous access balanced against the desire to preserve venous access.
- Any form of IV iron may be associated with potentially severe acute reactions. The symptoms of most concern are hypotension and dyspnea, which in the worst cases may be catastrophic with features of anaphylaxis. The cause of reactions has not been fully characterized, but may involve immune mechanisms and/or release of free, reactive iron into the circulation with induction of oxidative stress. The mechanisms of acute reactions may differ for different iron preparations. Certain iron dextrans in particular have been associated with reactions characteristic of anaphylaxis. The rate of such reactions is estimated to occur in 0.6%–0.7% of patients treated. The serious adverse effect event rate may be lower with low molecular weight iron dextran compared to high molecular weight iron dextran.
- Risks associated with blood transfusion include transfusion errors, volume overload, hyperkalemia, citrate toxicity (leading to metabolic alkalosis and hypocalcemia), hypothermia, coagulopathy, immunologically mediated transfusion reactions, including transfusion-related acute lung injury (TRALI), and iron overload, all of which are uncommon (see Table 5 in the original guideline document). Transmission of infections, although rare, is a major concern and this risk varies between countries (see Table 6 in the original guideline document).
- There may be toxicity from high doses of erythropoiesis-stimulating agents (ESA), as suggested, though not proven, by recent post-hoc analyses of major ESA randomized controlled trials, especially in conjunction with the achievement of high hemoglobin levels. Therefore, in general ESA dose escalation should be avoided. The Work Group suggestions for initial and acquired hyporesponsiveness imply that maximal doses should be no greater than four times initial weight-based appropriate doses.

## Contraindications

### Contraindications

Relative contraindications to an erythropoiesis-stimulating agent (ESA) include current or previous malignancy and previous stroke.

## Qualifying Statements

### Qualifying Statements

- This Clinical Practice Guideline document is based upon systematic literature searches last conducted in October 2010, supplemented with additional evidence through March 2012. It is designed to provide information and assist decision making. It is not intended to define a standard of care, and should not be construed as one, nor should it be interpreted as prescribing an exclusive course of management. Variations in practice will inevitably and appropriately occur when clinicians take into account the needs of individual patients, available resources, and limitations unique to an institution or type of practice. Every health-care professional making use of these recommendations is responsible for evaluating the appropriateness of applying them in any particular clinical situation. The recommendations for research contained within this document are general and do not imply a specific protocol.
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## Implementation of the Guideline

### Description of Implementation Strategy

An implementation strategy was not provided.

### Implementation Tools

Clinical Algorithm

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

## Institute of Medicine (IOM) National Healthcare Quality Report Categories

### IOM Care Need

Getting Better

Living with Illness

### IOM Domain

Effectiveness

Patient-centeredness

Timeliness

## Identifying Information and Availability

### Bibliographic Source(s)

Kidney Disease: Improving Global Outcomes (KDIGO) Anemia Work Group. KDIGO clinical practice guideline for anemia in chronic kidney disease. *Kidney Int Suppl.* 2012 Aug;2(4):279-335. [247 references]

### Adaptation

Not applicable: The guideline was not adapted from another source.

## Date Released

2012 Aug

## Guideline Developer(s)

Kidney Disease: Improving Global Outcomes - Nonprofit Organization

## Source(s) of Funding

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Kidney Disease: Improving Global Outcomes (KDIGO) Anemia Work Group

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## Financial Disclosures/Conflicts of Interest

Kidney Disease: Improving Global Outcomes (KDIGO) makes every effort to avoid any actual or reasonably perceived conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the Work Group. All members of the Work Group are required to complete, sign, and submit a disclosure and attestation form showing all such relationships that might be perceived or actual conflicts of interest. This document is updated annually and information is adjusted accordingly. All reported information is printed in the Biographic and Disclosure Information section of original guideline document and is on file at the National Kidney Foundation (NKF), Managing Agent for KDIGO.

## Guideline Status

This is the current release of the guideline.

## Guideline Availability

Electronic copies of the guideline: Available from the [Kidney Disease: Improving Global Outcomes \(KDIGO\) Web site](#) .

## Availability of Companion Documents

The following are available:

- KDIGO clinical practice guideline for anemia in chronic kidney disease. Appendices 1-2. New York: Kidney Disease: Improving Global Outcomes; 2012 Aug. 11 p. Electronic copies: Available in Portable Document Format (PDF) from the [Kidney Disease: Improving Global Outcomes \(KDIGO\) Web site](#) .
- KDIGO clinical practice guideline for anemia in chronic kidney disease. Online supplemental tables. New York: Kidney Disease: Improving Global Outcomes; 2012 Aug. 107 p. Electronic copies: Available in PDF from the [KDIGO Web site](#) .
- Methods for development of KDIGO clinical practice guidelines. Electronic copies: Available from the [KDIGO Web site](#) .

## Patient Resources

None available

## NGC Status

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